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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,090	01/22/2007	Yechezkel Barenholz	BARENHOLZ17	4718

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,090	BARENHOLZ ET AL.	
	Examiner	Art Unit	
	GOLLAMUDI S. KISHORE	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62,64,65,67,69-75 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62, 64-65, 67, 69-75 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/15/10;11/26/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

DETAILED ACTION

The amendment dated 11-26-10 is acknowledged.

Claims included in the prosecution are 62, 64-65, 67, 69-75 and 80.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 62, 64-65, 67, 69-75 and 80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of inflammation, does not reasonably provide enablement for treatment or prevention of diseases or disorder of mucosa. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d, 1400 (Fed.Cir.1988). Among these factors are: (1) the nature of the invention; 2) the state of the prior art; 3) the relative skill of those in the art; 4) the predictability or unpredictability of the art; 5) the breadth of the claims; 6) the amount of direction or guidance presented; 7) the presence or absence of working examples; and 8) the quantity of experimentation necessary. When the above factors are weighed, it is

the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) The nature of the invention: the invention concerns with administration of anionic liposomes containing a medicament for a disease or disorder of the GI (claim 62). The diseases include ulcerative colitis, Crohn's disease, irritable bowel syndrome, colon carcinoma and familial adenomatous polyposis (claims 69 and 75).

2) The state of the prior art: the state of the prior art is very high in terms of formulating the liposomal sustained release compositions and treating specific diseases using specific drugs and specific cancers using specific anti-cancer agents.

3) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high (Ph.D level technology).

4) The predictability or unpredictability in the art: It should be pointed out that the independent claim does not even recite a specific drug and the dependent claim recite drugs in generic terms and no specific anti-cancer drugs are recited although the dependent claims recite most drugs in generic terms and it is unclear which of these drugs treat which of the claimed diseases. With regard to colon carcinoma, the examiner cites Trosko (Mutation Research, 2001) as interest which shows that our current conventional approaches of cancer prevention/therapy have had limited success and in some cases such as treatment for pancreatic cancer, it has been a total failure. Trosko further teaches that we now know each organ specific tumor expresses different genes and furthermore, within a given tissue, no two tumors are genetically/phenotypically alike, it would be extremely naive to believe t hat all tumors

could be treated with some sort of a single therapy. According to Trosko, each phase of complex carcinogenic process represents cells at different genotypic/phenotypic stages and in addition, cancers are characterized by genetic instability and the excessive cell proliferation that give rise to cancers by multiple mechanisms through multiple pathways.

5). the breadth of the claims: instant claim is very broad in terms of diseases to be treated.

6) The amount of direction of guidance provided: instant specification does not provide adequate guidance in terms of the diseases claimed and the various active agents claimed.

7) The presence or absence of working examples: no working examples are provided for the effectiveness of anionic liposomes against the various diseases claimed.

8) The quantity of experimentation necessary: since as pointed out above, the generic term encompasses various diseases including colon carcinoma and one cannot determine the effectiveness of the claimed composition without undue experimentation.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that claims now have been limited to inflammation of the GI mucosa. This argument is not found to be persuasive since claim 75 still recites colon carcinoma and familial adenomatous polyposis which implies that applicant's intent is to include even these diseases in the inflammation. The rejection is still maintained.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 62, 64-65, 67, 69-75 and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant amends claim 62 to recite "in a manner and amount effective to achieve topical treatment of said GI mucosa. Line 3 of the claim 62 recites "administering to the gastrointestinal mucosa. This terminology is confusing since it is unclear as to how the composition is administered. Gastrointestinal system includes stomach, duodenum, small intestines and colon. How can one administer the composition topically to the GI mucosa? What does the term, 'in a manner' denote?

The dependent claim 69 for example recites nausea and reflux. It is unclear how these are mucosal diseases or conditions.

This rejection is maintained since applicant has not addressed this issue.

The meets and bounds of derivatives of 5-aminosalicylic acid are unclear.

Applicant's arguments with respect to 5-aminosalicylic acid derivatives that they are known in the art are not found to be persuasive. The reference of Travis submitted refers to one compound, sulfasalazine whereas instant claim recites 'derivative***s***. Claim 72 also recites sulfasalazine. It is unclear what other compounds come under the category of 'derivatives'.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 62, 64-65, 67, 69-75 and 80 are rejected under 35 U.S.C. 102(a) as being anticipated by Qi (US 2003/0095999).

Instant claim 62 recites the treatment of a disease or disorder of the mucosa by administering negatively charged liposomes loaded with active ingredients. Among the conditions recited are nausea, inflammation and colon carcinoma. Similarly instant claim 76 recites the prevention of a disease or condition of the mucosa

Qi teaches anionic liposomal compositions for the delivery of active agents within and/or beneath the mucosal membranes. The drugs encapsulated within the anionic liposomes include antibiotics, steroids, non-steroidal anti-inflammatory drugs such as prednisone, antiemetics, chemotherapeutic agents and vitamins (0023, 0038, 0039, 0049, 0081-0083, 0096, 0099-0102, 0126, 0145-0149). Since Qi teaches that the anionic liposomes deliver the active agents within the mucosa of the host treatment and prevention of the conditions such as inflammation, nausea and carcinoma are implicit in the teachings of Qi. Qi teaches vitamins which include antioxidant vitamins such as vitamin E and therefore, treatment of conditions relating to oxidative stress is implicit in Qi.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant argues the following:

> "The liposomes of Qi, being fusogenic, deliver the active ingredient via membrane fusion. In fact, Qi emphasizes transdermal delivery for systemic absorption. See paragraph [0130] of Qi ("Transdermal administration typically involves the delivery of a pharmaceutical agent for percutaneous passage of the drug into the systemic circulation of the patient." [Emphasis added]) and the claims of Qi, which clearly define that the delivery of the agent is "through the membrane." See also paragraph [0003] ("the present invention relates to methods for enhancing the transport and delivery of pharmaceutical agents across and/or within dermal and mucosal membranes") and paragraph [0070] ("the terms ~transport' and ~delivery' refers to the passage of a substance across or through the skin (i.e., transdermal), including the epidermis and dermis, or across a mucosal membrane, where the substance can contact, and be
>
> absorbed by the cells of that particular membrane."). Thus, Qi does not describe and even may be regarded as teaching away from topical (local) treatment, as is required by the present claims.
>
> Furthermore, saposin includes positively charged amino acids that are required for its association to the negatively charged phospholiposome membrane (see paragraphs [0090], [0091] and [0174] of Qi). Thus, one would expect that the fusogenic liposome is more zwitterionic than anionic. The present claims require that the lipid assemblies loaded with an active ingredient be negatively charged.
>
> While Qi refers to a variety of drugs that can be carried by the liposome, including anti-inflammatory drugs, there is no true example showing a therapeutic effect of the composition, all the more, an anti-inflammatory effect. All examples concentrate on the formation of the fusogenic liposomes."

These arguments are not persuasive. As The term, 'Gastrointestinal tract' includes, mouth, esophagus, stomach, small intestines and colon'. According to claim 62, the composition is administered to the gastrointestinal mucosa. In paragraphs 0145-0150 Qi discloses transmucosal delivery which includes even oral which instant claims

include. In 0146, Qi specifically teaches 'gastrointestinal'. Applicant thus, is incorrect in stating that Qi teaches only transdermal.

Applicant's arguments with regard to saposin are not persuasive since in paragraph 0027, Qi teaches that the amphipathic helices at amino and carboxyl termini of saposin C are inserted into the membrane and not the way applicant argues. Furthermore, instant claims only require that the lipid assemblies comprise negatively charged and that the active agent is not covalently bound. Qi satisfies both of these requirements. With regard to applicant's arguments that Qi lacks a true example showing therapeutic effect of the composition, the examiner points out that since the function of an anti-inflammatory drug is to treat inflammation, such a function is implicit. Similar is the case with claimed 'nausea' and colon carcinoma in claims 69 and 75 since Qi teaches antiemetics and chemotherapeutic agents; Furthermore, applicants themselves have not shown the efficacy of the composition against numerous disease conditions claimed which includes even colon carcinoma. Finally the examiner points out that instant claim 62 is drawn to 'a method of administering negatively charged liposomes and Qi teaches a method of administering negatively charged liposomes.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 62, 64-65, 67, 69-75 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qi cited above.

The teachings of Qi have been discussed above. Qi does not teach the treatment of all the diseases claimed through examples. However, in view of the suggestion of various active agents which could be incorporated and the guidance provided by Qi, it would have been obvious to one of ordinary skill in the art to prepare various compositions for the treatment of various diseases with a reasonable expectation of success.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Qi does not teach the specificity of negatively charged liposomes to inflamed mucosa and the unexpected benefits of such negatively charged liposomes in proving local and inflammation-targeted treatment of conditions within the GI tract. According to applicant, surprisingly the negatively charged liposomes adhered better to the inflamed colon than did cationic liposomes. This argument is not persuasive since instant claims are drawn to 'gastrointestinal mucosa' which implies the mucosa of esophagus, stomach, small intestines and colon and applicant's in vitro studies were done only with colon mucosal cells and no studies were done with the treatment of number diseases claimed. Just because the anionic liposomes adhere better to the ***inflamed*** mucosa of colon one cannot expect the anionic liposomes to treat even colon carcinoma. Furthermore, '***better*** adherence' to inflamed colon' does not make the claims patentable since Qi teaches 'anionic liposomes'. Furthermore, the prior art of

Haydon (Journal of cell biology) shows binding of the negatively charged liposomes to intestinal brush border myosin. The references of Baczynska (Verlag der Zeitschrift fur Naturforschung) and Kim (Arch. Pharm Res.) show the enhanced effect of negatively charged liposomes on colon carcinoma cells. These references are already of record. Therefore, applicant's arguments that the results are surprising are not persuasive.

9. Claim 67 is rejected under 35 U.S.C. 103(a) as being unpatentable over Qi cited above in combination with Iga (5,080,904) or Fossheim (US 2004/0170560, or Dyvik (US 2002/0039556) or Schneider (6,258,378) individually or in combination.

The teachings of Qi have been discussed above. Qi teaches the use of phosphatidylserine to form the anionic liposomes. Qi does not teach the use of phosphatidylglycerol or a saturated form of phosphatidylglycerol. The use of DSPG instead of phosphatidylserine taught by Qi would have been obvious to one of ordinary skill in the art since Iga, Fossheim, Dyvik and Schneider teach that for the preparation of liposomes either phosphatidylserine or phosphatidylglycerol could be used (see lines 35-56 of Iga; 0029 of Fossheim; 0031 of Dyvik and col. 4, lines 41-48 of Schneider).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that none of Iga, Fossheim, Dyvik or Schneider supplies the deficiencies of Qi or makes obvious the unexpected properties of the use of negatively charged loaded liposome assemblies for treatment of the GI mucosa. These arguments have been addressed above. The secondary references provide the motivation to use phosphatidylglycerol instead of phosphatidylserine taught by Qi and

applicant has not shown that results obtained using phosphatidylserine are different from results obtained using phosphatidylglycerol. The rejection is maintained.

8. Claims 62, 64-65, 67, 70, 72 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (Arch Pharm Res., 2000) or Baczynska (Verlag der Zeitschrift fur Naturforschung, 2001) of record.

Kim teaches in vitro cytotoxic effect of negatively charged liposomes containing (DSPG) on murine colon carcinoma cells (abstract, page 169, col. 1, in vitro Growth inhibition of C-26 cells).

Baczynska teaches surface charge and the association of liposomes with colon carcinoma cells. According to Baczynska when phosphatidylserine was incorporated into the lipid bilayer, the amount of liposomes associated with cells tended to increase along with the amount of negatively charged lipid present in the liposomal bilayer (abstract, page 874, negatively charged liposomes and discussion).

These references however, do not teach the administration of the liposomes or the mode of administration. However, since these references show the interaction of the liposomes to the colon carcinoma cells, it would have been obvious to one of ordinary skill in the art to choose an appropriate method of administration so that they reach the colon, interact with these cells and deliver the anticancer drugs.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S. KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK